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| 10/520,457 | 11/30/2005 | Caroline Connolly | FDEHN7.001APC | 5613 |

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| EXAMINER | |
|---|---|
| SCHUBERG, LAURA J | |

| ART UNIT | PAPER NUMBER |
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| 1657 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/520,457 | CONNOLLY ET AL. | |
| | Examiner | Art Unit | |
| | LAURA SCHUBERG | 1657 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7 and 14-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 14-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

This action is responsive to papers filed 11/20/2009.

Claims 1-7 and 14-29 are currently pending. Claims 1, 3, 16, and 21 have been amended. No claims have been newly added or newly canceled.

### *Previous Rejections*

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 1-6, 14, 16-19, 21-24, 26-29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kraus et al (US 5,143,838) in view of Piet et al (Transfusion 1990) and Anderle et al (US 2003/0133829).**

Claim 1 is drawn to a method for the preparation of virus-inactivated thrombin comprising

a) subjecting a solution comprising prothrombin and factor X to a virus inactivation procedure, by adding solvent and detergent to the solution, wherein the solvent is tri-n-butyl phosphate;

b) loading the product of step a) onto an anion exchange medium;

c) washing the anion exchange medium to remove reagents used for the virus inactivation in step a); and

d) activating the prothrombin on the anion exchange medium to form thrombin by addition of metal ions, wherein a fraction of the thrombin has a specific activity of at least 2000 International Units per mg of protein.

Dependent claims include wherein the solution is prothrombin complex (claim 2), the type of metal ions (claims 4 and 5), further comprising the steps of e) selectively eluting the thrombin from the anion exchange medium (claim 6) and wherein step d is performed without the addition of phospholipids (claims 26).

Claim 3 is drawn to a method for the preparation of virus-inactivated thrombin comprising

a) subjecting a solution comprising factor X to a virus inactivation procedure, by adding solvent and detergent to the solution wherein the solvent is tri-n butyl phosphate;

b) loading the product of step a) onto an anion exchange medium;

c) washing the anion exchange medium to remove reagents used for virus inactivation of step a); and

d) activating the factor X on the anion exchange medium to form factor Xa by addition of metal ions; and

e) loading virus-inactivated prothrombin onto the anion exchange medium such that thrombin is generated, wherein a fraction of the thrombin has a specific activity of at least 2000 International Units per mg of protein.

Dependent claims include the type of metal ions (claims 4 and 5), replacing steps a) and b) with steps a') and b') wherein a') is loading a solution comprising prothrombin and factor X onto an anion exchange medium and b') is solvent-detergent virus

inactivating of the prothrombin and factor X on the anion exchange medium (claim 8), further comprising the step of f) selectively eluting the thrombin from the anion exchange medium (claim 14) and wherein step d is performed without the addition of phospholipids (claims 27).

Claims 16 and 21 are drawn to a method for the preparation of virus inactivated thrombin comprising replacing steps a) and b) with steps a') and b') wherein a') is loading a solution comprising prothrombin and factor X onto an anion exchange medium and b') is subjecting the prothrombin and factor X to a virus inactivation procedure by adding solvent and detergent to the prothrombin and factor X on the anion exchange medium, wherein the solvent is tri-n butyl phosphate, step c is washing the anion exchange medium to remove reagents used for the virus procedure in step b wherein claim 16 requires activating prothrombin in step d and claim 21 requires activating factor X in step d such that a fraction of thrombin has a specific activity of at least 2000 International Units per mg of protein.

Dependent claims include the type of metal ions (claims 17, 18, 22, 23), further comprising the steps of e) selectively eluting the thrombin from the anion exchange medium (claims 19 and 24) and wherein step d is performed without the addition of phospholipids (claims 28-29).

Kraus et al teach a method of producing thrombin from prothrombin using calcium ions for the conversion on an anion exchange medium. This includes a solution, preferably human blood plasma or a fraction thereof, that contains Factor II (prothrombin) is adsorbed onto an anion exchange medium (column 2 lines 26-36). For

elution a buffer that contains an activator –calcium ions, calcium ions plus thromboplastin or Factor Xa are applied to the matrix. The plasma or plasma fraction is activated into thrombin with the buffer solution by eluting the matrix (column 2 lines 37-49). Filtration of the thrombin is suggested and taught to increase purity (column 2 lines 58-61). Before or after the thrombin is isolated from the plasma or plasma fraction the batch can be sterilized to inactivate human-pathogenic viruses by treatment with detergent or by heating (column 3 lines 1-7). Phospholipids are not taught to be required.

Kraus et al do not teach solvent-detergent inactivation on the anion exchange medium or freeze-drying the thrombin product. Kraus et al do not specifically sterilize the plasma prior to fractionation.

Piet et al teach that since treatment with TNBP (tri-n butyl phosphate) and detergent mixtures did not interfere with plasma fractionation, sterilization methods can be applied at the time of plasma collection, prior to fractionation procedures, which would enhance safety in the fractionation center and simplify process methodology (page 597, column 1). If desirable, products prepared from TNBP-treated plasma can be subjected to additional virucidal procedures (abstract).

Therefore one of ordinary skill in the art would have been motivated to sterilize the plasma in the method of Kraus et al prior to obtaining fractions because Piet et al teach that sterilization methods can be applied at the time of plasma collection, prior to fractionation procedures, which would enhance safety in the fractionation center and simplify process methodology (page 597, column 1). One of ordinary skill in the art

would have had a reasonable expectation of success because Piet et al was successful with obtaining fractions of plasma with this order of steps (page 595, table 2).

Anderle et al teach a process for inactivating pathogens in a biological material. The solvent-detergent virus inactivating of a protein solution, the subsequent adsorption to an anion exchange medium (DEAE sephadex), washing of the protein loaded anion exchange medium, elution of the proteins and filtration are taught (pages 7-8, examples 4 and 7). In addition to protein enrichment steps, the protein may also be purified either before or after the treatment disclosed (page 5 para 58). Exemplary proteins include coagulation factors such as FII (prothrombin) and FX and FEIBA (activated prothrombin complex concentrate) (page 5 para 57 and page 6 para 66). The method is taught to be a gentle, effective procedure for inactivating pathogens in a protein solution, which does not substantially reduce the activity of a selected protein in the solution (page 2 para 12).

Therefore, one of ordinary skill in the art would have been motivated to apply the solvent-detergent inactivating steps of Anderle et al to the method of Kraus et al because Anderle et al teach that these steps are a gentle, effective procedure for inactivating pathogens in a protein solution, which does not substantially reduce the activity of a selected protein in the solution (page 2 para 12) and Kraus et al had also suggested using detergent to inactivate viruses (column 3 lines 1-7). One of ordinary skill in the art would have had a reasonable expectation of success of combining these methods because both Kraus et al and Anderle et al were teaching the purification of proteins such as plasma fractions.

M.P.E.P. § 2144 recites, "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law…If the facts in a prior legal decision are sufficiently similar to those in an application under examination, the examiner may use the rationale used by the court." In *In re Burhans, 154 F.2d 690, 69 USPQ 330* (CCPA 1946), the court found that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. In *In re Gibson, 39 F.2d 975, 5 USPQ 230* (CCPA 1930), the court found that selection of any order of mixing ingredients is *prima facie* obvious.

The limitation regarding the specific activity of the prothrombin fraction being at least 2000 International Units per mg of protein is deemed to be a property found in the final product upon performance of the obvious method steps.

Therefore the combined teachings of Kraus et al, Piet et al and Anderle et al render obvious Applicant's invention as claimed.

**Claims 7, 15, 20 and 25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kraus et al (US 5,143,838) in view of Piet et al (Transfusion 1990) and Anderle et al (US 2003/0133829) as applied to claims 1-6, 14, 16-19, 21-**

**24 and 26-29 above, and further in view of Kingdom et al (US 5,354,682) and Heimburger et al (US 6,346,277).**

Claim 7 is drawn to the method of claim 6 further comprising the steps of f) passing the product of step e) through a filter which retains pathogens, step g) adding a divalent metal ion and a carbohydrate to the product of step f), step h) freeze-drying and heat-treating the product of step g) to inactivate viruses.

Claim 15 is drawn to the method of claim 14, further comprising the steps of g) passing the product of step f) through a filter which retains pathogens, h) adding a divalent metal ion and a carbohydrate to the product of step g), step i) freeze-drying and heat-treating the product of step h) to inactivate viruses.

The combined teachings of Kraus et al, Piet et al and Anderle et al render obvious Applicant's invention as claimed as described above. Heat treatment is suggested by Kraus et al as a suitable method for sterilization of the thrombin product (column 3 lines 1-7).

Kingdom et al teach that after elution from a capture means thrombin may be further processed through lyophilization, ultrafiltration and other conventional methods. Stability of the final thrombin product is enhanced by infusion of starch, dextran, or combinations thereof (carbohydrates) and packaged for drug use (column 5 line 64-column 6 line 7).

Heimburger et al teach that to destroy the hepatitis viruses in a blood plasma fraction it is beneficial to add calcium ions and sucrose to a blood plasma fraction prior to heat treatment to increase the stability of the final product (column 5 lines 25-30). The

product subject to this treatment can also be supplied in freeze-dried form as well (column 6 lines 34-40).

Therefore one of ordinary skill in the art would have been motivated to freeze-dry the thrombin product of Kraus et al because Kingdom et al teach that it is suitable to do so and would have allowed the thrombin to be stored for long periods of time. One of ordinary skill in the art would have been motivated to add agents (such as carbohydrates) to enhance the stability of the thrombin product because Kingdom et al suggests that it is beneficial to do so. One of ordinary skill in the art would have been motivated to add calcium ions with a carbohydrate such as sucrose because Heimburger et al teach that these agents will increase the stability of a blood plasma fraction upon heat treatment for the killing of hepatitis viruses. One of ordinary skill in the art would have had a reasonable expectation of success because the references are all drawn to increasing the sterility and stability of blood plasma fractions and because Piet et al and Kingdom et al teach that conventional methods may be used to further process the thrombin product.

Therefore the combined teachings of Kraus et al, Piet et al, Anderle et al, Kingdom et al and Heimburger et al render obvious Applicant's invention as claimed.

## ***Response to Arguments***

Applicant's arguments filed 11/20/2009 have been fully considered but they are not persuasive.

Applicant argues that the Piet reference does not disclose the production of a thrombin fraction. Applicant asserts that Piet is actually referring to the production of prothrombin and not thrombin. Applicant asserts that Piet relates only to the detection of native proteins in plasma.

This is found persuasive as Factor II as disclosed in table 2 of Piet can also refer to prothrombin. However this does not negate the teaching of Piet wherein sterilization methods can be applied at the time of plasma collection, prior to fractionation procedures, which would enhance safety in the fractionation center and simplify process methodology (page 597, column 1). Piet is most definitely concerned with improving the viral safety of blood products and coagulation factor concentrates (page 591 column 1) and provides sufficient motivation and reasonable expectation of successfully modifying the order of the steps used for viral inactivation of blood products.

Applicant argues that Anderle et al teaches that prothrombin is deactivated by conventional solvent-detergent methods.

This is not found persuasive because Anderle et al teaches that the inactivation method is a gentle, effective procedure for inactivating pathogens in a protein solution, which does not substantially reduce the activity of a selected protein in the solution (page 2 para 12). In addition Piet teaches that treatment with TNBP and detergent inactivates viruses in purified blood protein solutions while allowing high retention of the biologic activity of the proteins (page 595, Discussion). Clearly Piet and Anderle et al

are concerned with preserving the biological activity of the protein fractions such as prothrombin while inactivating the pathogens as well.

Applicant argues that Piet teaches methods that are not suitable for the fractionation of the prothrombin complex coagulation factors and would not be an obvious choice for a skilled person with regard to generation of thrombin.

This is not found persuasive because this argument is merely the argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964): and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). Piet clearly states that that treatment with TNBP and detergent inactivates viruses in purified blood protein solutions while allowing high retention of the biologic activity of the proteins (page 595, Discussion) and this would motivate one of ordinary skill in the art to use this treatment for the prothrombin fraction in the method of Kraus et al as described above.

Applicant argues that Anderle et al teaches the use of a carboxylic acid ester for the S/D inactivation step whereas the presently amended claims use tri-n-butyl phosphate.

This is not found persuasive because Piet teaches the use of tri-n-butyl phosphate (TNBP) as a beneficial solvent for S/D treatment (page 595 Discussion).

Applicant argues that Anderle et al teaches away from the presently claimed method by stating that the conventional S/D treatment at least partially deactivates

prothrombin. Applicant asserts that Anderle et al recommends the use of detergent alone be used at high concentrations and cites paragraph 5 as evidence.

This is not found persuasive because paragraph 5 of Anderle et al is part of the background of the Anderle et al reference and does not in fact recommend using detergent alone for the treatment of prothrombin but discusses the problems with the solutions used in the past regarding prothrombin treatment. Anderle et al suggest that Tween 80 is a conventional detergent that if used alone produces unsatisfactory results (paragraphs 5-7) and goes on to suggest that there are inactivation methods that produce improved results (page 2 paragraphs 12-14).

Applicant argues that the present invention provides significant unexpected results as compared to the Kraus method. Applicant asserts that the presently claimed invention provides both a purity and concentration of thrombin which are surprisingly better than those achieved by the Kraus reference.

This is not found persuasive because one of ordinary skill in the art would expect to gain improved results for the Kraus et al method by adding the purification techniques of Piet and Anderle et al. Anderle et al state that their protein purification method has surprisingly shown that pathogens in a protein solution are effectively inactivated, while the protein activity is substantially preserved (page 2 para 14). In addition, the examples that Applicant cites as evidence for unexpected results include additional elements that are not included in the invention as claimed and are therefore not commensurate in scope. In addition, the starting amounts used for the methods would appear to affect the yield produced as well and should be taken into consideration.

In submitting evidence asserted to establish unobvious results, there is a burden on an applicant to indicate how the examples asserted to represent the claimed invention are considered to relate to the examples intended to represent the prior art and, particularly, to indicate how those latter examples do represent the closest prior art. See *In re Borkowski*, 595 F.2d 713, 184 USPQ 29 (CCPA 1974); *In re Goodman*, 339 F.2d 228, 144 USPQ 30 (CCPA 1964).

The evidence relied upon should also be reasonably commensurate in scope with the subject matter claimed and illustrate the claimed subject matter "as a class" relative to the prior art subject matter "as a class." *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971); *In re Hostettler*, 429 F.2d 464, 166 USPQ 558 (CCPA 1970). See, also, *In re Lindner*, 457 F.2d 506, 173 USPQ 356 (CCPA 1972).

It should also be established that the differences in the results are in fact unexpected and unobvious and of both statistical and practical significance. *In re Merck*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Klosak*, 455 F2d 1077, 173 UAPQ 14 (CCPA 1972); *In re D'Ancicco*, 429 F.2d 1244, 169 USPQ 303 (CCPA 1971). *Ex parte Gelles*, 22 USPQ2d 1318 (BPAI 1992).

Therefore the claims remain rejected as cited above.

## ***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg